Journal of Neurology (2019) 266:157–164
https://doi.org/10.1007/s00415-018-9113-3

ORIGINAL COMMUNICATION

Non-invasive evaluation of cerebral perfusion in patients with transient ischemic attack: an fMRI study

Yating Lv[1,2,3] · Wei Wei[1,2,3] · Yulin Song[3] · Yu Han[4] · Chengshu Zhou[3] · Dan Zhou[3] · Fuding Zhang[3] · Qiming Xue[5] · Jinling Liu[6] · Lijuan Zhao[3] · Cairong Zhang[3] · Lingyu Li[1,2,3] · Yu-Feng Zang[1,2,3] · Xiujie Han[3]

Received: 12 October 2018 / Revised: 2 November 2018 / Accepted: 2 November 2018 / Published online: 16 November 2018

Abstract

Detection of hypoperfused tissue due to the ischemia is considered to be important in understanding the cerebral perfusion status and may be helpful in guiding therapeutic decisions for patients with transient ischemic attack (TIA). We hypothesized that the combination of two non-invasive fMRI techniques: resting-state BOLD-fMRI time-shift analysis (TSA) approach and 3D ASL, could detect the cerebral hemodynamic status in TIA patients noninvasively. From April 2015 to June 2016, 51 TIA patients were recruited in this study. We calculated the time delay between the resting-state BOLD signal at each voxel and the whole-brain signal using TSA approach and compared the results to CBF map derived from ASL. Out of the 51 patients, 24 patients with normal arrival time and CBF were in Stage 0; 14 patients who showed delayed arrival time and normal CBF which indicated elevated CBV were in Stage I; the other 13 patients who had both delayed arrival time and decreased CBF were in Stage II, the group average spatial overlap, i.e., Dice coefficient, of the two measurements was 0.55. Four patients in Stage 0 (17.4%), three patients in Stage I (23.1%) and five patients in Stage II (45.5%) suffered ischemic stroke or TIA symptoms in 1 year after MRI scan. The patients in Stage II was at highest risk of subsequent events when compared to other two stages. The combination of resting-state BOLD-fMRI and ASL hold the potential to noninvasively identify the hemodynamic status in TIA patients and help predict the risk of subsequent events.

Keywords Perfusion · Resting-state fMRI · Arterial spin labeling · Time-shift analysis · Transient ischemic attack · Cerebral blood flow

Introduction

Transient ischemic attack (TIA) is a transient episode of neurologic deficit(s) caused by transient ischemia of the eloquent brain, the symptoms of a TIA can resolve within a few minutes or within 24 h. TIA is an important risk factor for eventually stroke or a silent stroke [1, 2]. Purely clinical scales, such as the ABCD2 score which considers age, blood pressure, clinical features, duration of symptoms, and history of diabetes [3], can identify patients at high risk of subsequent stroke. Brain imaging techniques are increasingly used to objectively identify true TIA which is presumed to have a vascular etiology [4]. Diffusion-weighted imaging (DWI) is positive among 30% of the patients referred for the evaluation of TIAs [5], and significantly improves the ability to predict subsequent events [6–9]. Recent studies have indicated that many TIA patients also have perfusion deficits using dynamic susceptibility contrast-enhanced perfusion-weighted imaging (DSC-PWI) or CT perfusion

✉ Xiujie Han
ashanxj@163.com

1 Institutes of Psychological Sciences, Hangzhou Normal University, Hangzhou 311121, Zhejiang, China

2 Zhejiang Key Laboratory for Research in Assessment of Cognitive Impairments, Hangzhou 311121, Zhejiang, China

3 Department of Neurology, Anshan Changda Hospital, No. 69 Changda St, Tiedong District, Anshan 114005, Liaoning, China

4 Department of Neurology, the First Affiliated Hospital, Dalian Medical University, Dalian 116011, Liaoning, China

5 Department of Image, Anshan Changda Hospital, Anshan 114005, Liaoning, China

6 Department of Ultrasonics, Anshan Changda Hospital, Anshan 114005, Liaoning, China

(CTP) [10–15]. It has been hypothesized that TIA patients with perfusion deficits, even in the absence of DWI changes, may be at higher risk of subsequent events [16]. Therefore, detection of hypoperfused tissue due to the ischemia is considered to be important in understanding the cerebral perfusion status and may be helpful in guiding therapeutic decisions for patients with TIA.

DSC-PWI and CTP are the most commonly used in clinical practice to assess the cerebral perfusion deficit in patients with TIA. Maps of cerebral blood flow (CBF), blood volume (CBV), time to peak (TTP) and mean transit time (MTT) are calculated to evaluate hemodynamic status which supposed to have three different stages after brain ischemia [17]. Stage 0: CBF is closely matched to the resting metabolic rate of the tissue, the brain can maintain resting balance between blood flow and metabolism; Stage I: cerebrovascular autoregulation, the intravascular CBV is elevated; Stage II: the capacity for compensatory vasodilation is exceeded, autoregulation fails, and CBF begin to decline. However, the major drawback of CTP and DSC-PWI is that it requires contrast agent which comes with potentially severe side-effects and precludes repetitive examinations for monitoring purposes. Noninvasive alternatives are being sought to give the similar pathophysiological information as CTP and DSC-PWI without the need for contrast agents.

Arterial spin labeling (ASL) uses water molecules in blood as intrinsic diffusion marker for noninvasive quantification of brain perfusion [18]. ASL has been applied to identify the perfusion deficits in patients with TIA and proved to be effective [19–22]. Recent study has shown that ASL could more frequently detect hypoperfused brain regions compared with DSC-PWI [22]. However, ASL have poor signal to noise ratio [13] and single measurements of CBF alone do not adequately assess cerebral hemodynamic status [23].

Resting-state functional magnetic resonance imaging using blood oxygenation level-dependent (BOLD-fMRI) is a noninvasive imaging technique which does not require contrast agent infusion and still maintains high temporal resolution. Previous study indicated that an assessment of time delays of the spontaneous low-frequency fluctuations of the BOLD signal may provide cerebral perfusion information, and thus serve as a noninvasive alternative to monitor perfusion changes. Recently, this approach, time-shift-analysis (TSA), has been applied to ischemic stroke [24–27] and chronic hypoperfusion patients [28], and the time delay areas were proved to be comparable to MTT or TTP map from DSC-PWI.

Following the facts that the TSA of resting-state BOLD-fMRI can provide arrival time information of cerebral perfusion and ASL can noninvasively quantify the CBF, we hypothesized that combination of two non-invasive fMRI techniques: resting-state BOLD-fMRI and 3D ASL, could detect the cerebral hemodynamic status in TIA patients non-invasively, and could, therefore, help increase the accuracy and confidence in clinical diagnosis. We also predicted that the risk for subsequent events is higher in Stage II than other two stages for patients with TIA.

Materials and methods

Participants

From April 2015 to June 2016, 51 patients with TIA (age = 30–79 years; 40 males) who had transient neurologic symptoms due to a possible vascular etiology (as evaluated by experienced clinical neurologists) were recruited from the Department of Neurology, Anshan Changda Hospital. Patients with hemorrhage, leukoaraiosis, epilepsy, migraine or a history of psychiatric disease were excluded from this study. For each patient, we recorded the following information: (1) history of TIA and stroke; (2) risk factors including hypertension, diabetes mellitus, coronary artery disease, current smoking and drinking; (3) medications used before the MR scanning; (4) in-hospital evaluation of arterial stenosis (carotid duplex ultrasound and MR angiography (MRA)), atrial fibrillation (electrocardiogram) and brain infarcts (diffusion-weighted imaging and T2-FLAIR); (5) 1-year telephone follow-up of stroke and/or TIA. ABCD2 score was obtained for each patient to evaluate the risk for subsequent stroke. All patients completed a series of physiological and biochemical tests within 24 h before the MR scanning, including blood systolic pressure, blood diastolic pressure, blood sugar level, cholesterol. Additionally, all patients underwent the mini-mental state examination (MMSE) to evaluate global cognition [29]. This study was approved by the Ethics Committee of the Center for Cognition and Brain Disorders, Hangzhou Normal University. Written informed consent was obtained from each participant.

MR data acquisition

All MRI data were acquired using a GE MR-750 3.0 T scanner (GE Medical Systems, Waukesha, WI) at Anshan Changda Hospital. The time intervals between the last TIA and the MRI scanning were from 6 h to 16 days. During the data acquisition, the participants were instructed to keep awake, relax with their eyes closed and remain motionless as much as possible.

(1) Resting-state BOLD-fMRI data were acquired using an echo-planar imaging sequence: 43 axial slices, repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, matrix = 64×64, field of view (FOV) = 220×220 mm^2, thickness/gap = 3.2/0 mm and flip angle = 60°. This session consisted of 240 contiguous volumes and lasted for 8 min;

(2) The 3D ASL data were acquired using a pseudo continuous ASL 3D fast-spin echo encoded spiral readout imaging sequence: 45 axial slices, TR = 4781 ms, TE = 11.12 ms, matrix size = 128 × 128, FOV = 220 × 220 mm^2, thickness/gap = 3/0 mm, points = 512, arms = 12, labeling duration = 1500 ms and post-label delay = 1525 ms. The session lasted for about 7 min.

Data preprocessing

Resting-state BOLD-fMRI data was processed using toolbox: REST-Time Shift Analysis (https://github.com/K-Z-W/Time_Shift_Analysis, developed by Yating Lv and Wei Wei) which includes two modules: resting-state BOLD-fMRI data preprocessing and time-shift analysis (TSA). The process of each dataset only needs 3 min.

Preprocessing of BOLD-fMRI data in REST-Time Shift Analysis toolbox calls the functions from RESTplus (http://restfmri.net/forum/RESTplus V1.2), including (1) discarding the first 10 volumes of functional images to make the longitudinal magnetization reach steady state and to let the participant get used to the scanning noise; (2) slice timing to correct the differences in image acquisition time between slices; (3) head motion correction; (4) spatial smoothing with a Gaussian kernel with a 6-mm full width at half maximum; (5) removing the linear trend of the time course; (6) regressing out the head motion effect (using six motion parameters: three rigid body translations and three rotations) from the fMRI data; and (7) band-pass (0.01–0.08 Hz) filtering. No patients were excluded from further analysis due to large head motion (more than 3.0 mm of maximal translation (in any direction of x, y or z) or 3.0° of maximal rotation throughout the course of scanning).

CBF maps from ASL were created using FuncTool software on the GE workstation and then were coregistered to the individual's mean BOLD-fMRI images using the utility from REST-Time Shift Analysis toolbox.

Time-shift analysis (TSA)

TSA of the preprocessed resting-state BOLD-fMRI data was performed according previous work [26]. We calculated the average time series across the whole brain as the reference time course. For each voxel, we shifted the time course from − 3 TR to 3 TR (− 6.0 to + 6.0 s), and correlated it with the reference time course at each TR. Each voxel was then assigned a value based on the time-shift required to reach the maximal correlation coefficient.

Clinical validation

Two professional radiologists (N.L. and C.Q, with 4 and 5 years of experience, respectively) who were blinded to the patients information independently traced the hypoperfusion regions (presence of focal slow flow (decreased CBF) in a vascular distribution) and time delay areas of TSA results for each patient. One traced the masks based on the CBF maps from ASL, and the other traced masks based on TSA delay results. Overlap was calculated using the Dice coefficient (DC), which calculates the ratio of the intersection with respect to the union of each pair of masks.

Results

All the demographic and clinical information are summarized in Table 1. Out of the 51 patients, 4 (7.8%) experienced stroke, 25 (52.1%) experienced TIA, 23 (54.9%) were first-episode, 6 (11.8%) had small infarcts in white matter, and 10 (19.6%) had intracranial large-vessel stenosis or carotid artery stenosis. The median ABCD2 score for the TIA patients was 4 (2–6). Four patients dropped out in one-year follow-up. Out of the 47 patients who had 1-year follow-up information, 12 patients experienced follow-up TIA or stroke attack (only one patient experienced both TIA and stroke attack), 1 patient had recurrent stroke.

Table 1 Demographics and clinical characteristics of patients with TIA (n = 51)

	TIA ($n = 51$)
Age (years)	30–79 (57.4 ± 9.5)
Sex (M/F)	40/11
MMSE	15–30 (29.3 ± 2.5)
Blood systolic pressure (mmHg)	100–200 (145.6 ± 20.7)
Blood diastolic pressure (mmHg)	60–110 (86.7 ± 10.3)
Blood sugar level (mmol/L)	4.3–16.2 (6.3 ± 2.1)
Total cholesterin (mmol/L)	3.5–8.1 (5.3 ± 1.1)
ABCD2 scores, median	4 (2–6)
Smoking, No. (%)	33 (64.7%)
Drinking, No. (%)	24 (47.1%)
Hypertension, No. (%)	25 (49%)
Diabetes, No. (%)	8 (15.7%)
Coronary artery disease, No. (%)	4 (7.8%)
Atrial fibrillation, No. (%)	1 (2.0%)
Medication	
Antiplatelets, No. (%)	51 (100%)
Statins, No. (%)	2 (3.9%)
DWI hyperintensity, No. (%)	6 (11.8%)
Vessel stenosis (> 50% stenosis), No. (%)	10 (19.6%)
TIA/stroke attack in 1-year follow-up, No. (%)	12 (25.5%)[a]

TIA transient ischemic attack, *M* male, *F* female, *MMSE* mini-mental state examination, *DWI* diffusion weighted imaging

[a]Four patients dropped out in the 1-year follow-up

Twenty-four patients with TIA who had no obvious perfusion deficits in CBF maps showed no time delay area in TSA results. There were some narrow areas in intracranial large-vessel but no severe intracranial large-vessel confirmed by MRA or carotid artery stenosis/occlusion identified by carotid duplex ultrasound examination in these patients. The results suggested that the hemodynamic status was in Stage 0 in these patients. Cerebral perfusion still could maintain resting balance between blood flow and metabolism. In these twenty-four patients, one dropped out in 1-year follow-up; four patients (17.4%) had subsequent events in 1 year after scanning (2 had ischemic stroke attack, 1 had TIA, 1 had both ischemic stroke attack and TIA).

Fourteen patients (A1-A14) with TIA without obvious decreased CBF showed time delay areas from TSA (Fig. 1). Patient A3 showed time delay (from TSA) but increased CBF in temporal lobe. The high DWI signal which suggested ischemia in the same area confirmed our TSA results. Four patients (A2, A5, A7, A13) had intracranial large-vessel severe stenosis confirmed by MRA or carotid artery stenosis/occlusion identified by carotid duplex ultrasound examination, while the other ten patients had some narrow areas in intracranial large-vessel. Patient A2 had severe stenosis in left carotid artery (MCA) on MRA. TSA demonstrated pronounced comparable time delay areas in the left MCA's corresponding blood supply area, while the CBF had no difference between two hemispheres. Patient A5 who had severe stenosis in left carotid artery identified by carotid duplex ultrasound examination showed pronounced time delay areas in the corresponding blood supply area. Five patients (A7, A11, A12, A13, A14) who had bilateral intracranial large-vessel or carotid artery lesions showed time delay areas in both hemispheres. With delayed arrival time and relative normal CBF the CBV should elevate in time delay areas from TSA, which suggested that hemodynamic status was in Stage I of cerebrovascular autoregulation in these patients. One patient dropped out in 1-year follow-up; three patients (23.1%) had ischemic stroke in 1 year after scanning.

The other thirteen patients (B1–B13) showed time delay areas from TSA which were comparable to decreased blood flow regions on CBF maps from ASL (Fig. 2). The volumetric and the overlap between two measurements results were listed in Table 2. The group average spatial overlap, i.e., Dice coefficient (DC), of the two measurements was 0.55. A relatively low degree of overlap (DC = 0.21) in patient B5 was likely caused by many spikes in the head motion curve

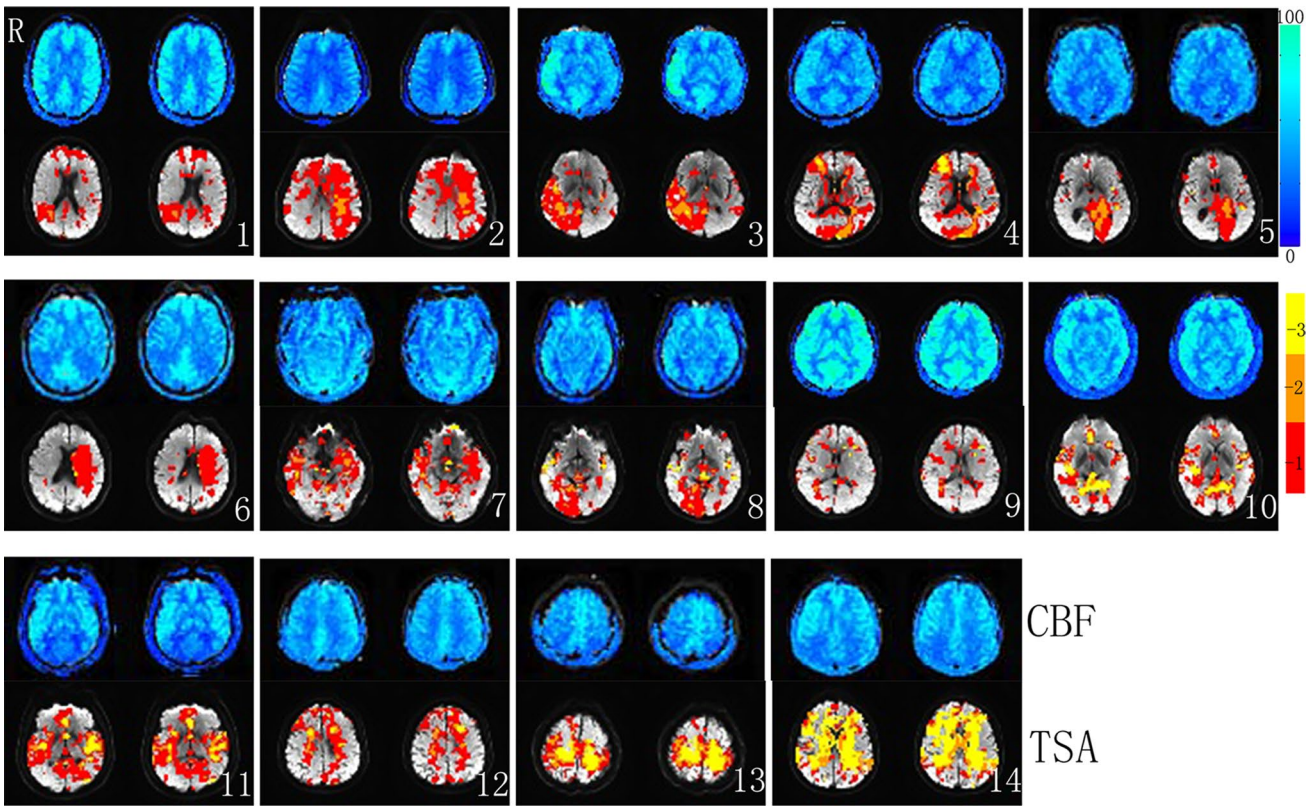

Fig. 1 TSA time delay results and CBF of fourteen TIA patients (A1-A14). Patients showed a pronounced time delay to the global mean time course (bottom row) in some brain regions but without obvious decreased blood flow in CBF map (upper row). −1, −2, −3 in color bar indicate −1TR, −2TR, −3 TR time shift. TSA: time-shift analysis; CBF: cerebral blood flow

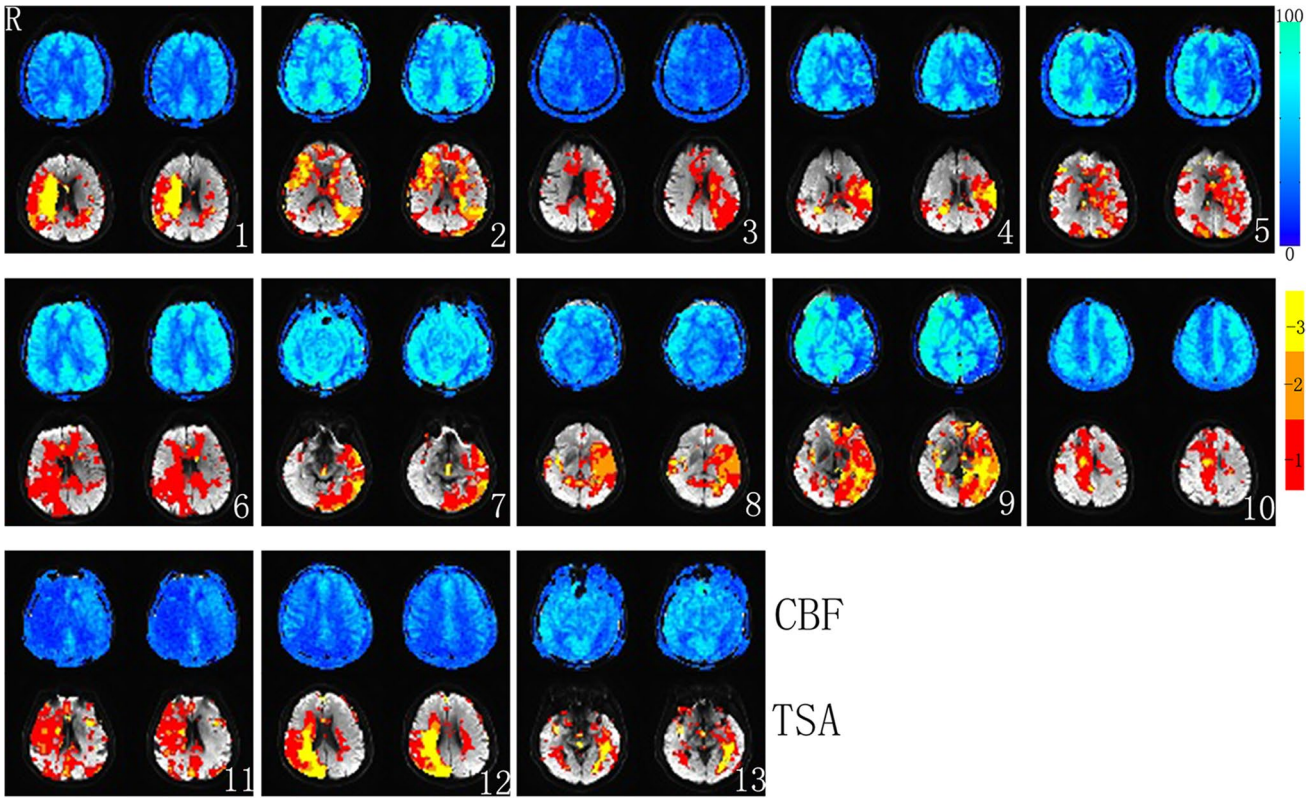

Fig. 2 TSA time delay results and CBF of thirteen TIA patients (B1–B13). The areas showed a pronounced time delay to the global mean time course (bottom row) were very similar to hypoperfusion region in CBF map (upper row). −1, −2, −3 in color bar indicate −1TR, −2TR, −3 TR time shift. *TSA* time-shift analysis, *CBF* cerebral blood flow

Table 2 The overlap between TSA delay results and CBF maps for 13 patients in Stage II of hemodynamic status

Patient no.	TSA temporal delay voxel number	CBF decrease voxel number	Overlap (DC)
B1	5629	5233	0.69
B2	4040	2252	0.58
B3	4610	8690	0.56
B4	5283	6047	0.76
B5	2678	2502	0.21
B6	2650	2127	0.48
B7	5334	4326	0.62
B8	3308	3103	0.62
B9	7292	10,600	0.57
B10	2131	1525	0.54
B11	6972	7018	0.53
B12	4943	4329	0.58
B13	1961	2302	0.41

TSA time-shift analysis, *CBF* cerebral blood flow, *DC* dice coefficient

of this patient. Six out of thirteen patients (B1, B3, B6, B8, B9, B11) had severe intracranial large-vessel stenosis/occlusion confirmed by MRA or carotid artery stenosis/occlusion identified by carotid duplex ultrasound examination, while the other seven patients had some narrow areas in intracranial large-vessel. TSA demonstrated pronounced time delay areas in corresponding blood supply area in six patients who had severe artery stenosis (B1 in right MCA, B3 and B9 in left carotid artery, B6 and B11 in right carotid artery, B8 in left MCA,), while the CBF also decreased in corresponding areas. With decreased CBF the results indicated that the capacity for compensatory vasodilation is exceeded and autoregulation failed, which suggested that hemodynamic status was in Stage II in these patients. Two patients dropped out in 1-year follow-up; five patients (45.5%) had subsequent events in 1 year after scanning (4 had ischemic stroke attack, 1 had TIA).

Discussion

In this study, we successfully combined two non-invasive fMRI techniques, resting-state BOLD-fMRI and ASL, to identify hypoperfused areas in patients with TIA. We suggest that the combination of an assessment of time delays of the spontaneous low frequency fluctuations of the BOLD signal and the mean cerebral blood flow (CBF) may provide

information of hemodynamic status, and thus serve as non-invasive diagnostic tools for TIA without the need for the application of the contrast agent.

Grubb and colleagues [17] proposed three stages of hemodynamic status changes of brain ischemia: Stage 0 characterizes normal CBF, Stage I characterizes elevated CBV, while CBF decrease in Stage II. Single measurements of CBF alone do not adequately assess cerebral hemodynamic status. Low frequency fluctuations of resting-state BOLD signals usually reflect spontaneous neuronal activity [30, 31]. Moreover, the BOLD signals contain information concerning local blood flow and oxygen consumption [32], thus impaired hemodynamic status or severity of hemodynamic impairment could be assessed by evaluating the changes in BOLD response, which can be absent, reduced, negative or delayed (temporal shift/lagged) [33, 34]. Time-shift analysis (TSA) of resting-state BOLD signal was defined as the temporal shift required to the maximal correlation with reference time course (i.e., the global mean of the brain). Such an approach has recently been used to assess pathophysiological events associated with hemodynamics and provided a high spatial correspondence on the individual level with the area of hypoperfusion as defined by DSC-PWI without the application of contrast agent [24–28]. Thus, the combination of two fMRI techniques: TSA of resting-state BOLD-fMRI can provide the arrival time information of blood flow and the ASL can noninvasively quantify the CBF, could evaluate the hemodynamic status change of brain ischemia.

The major finding in our present study was that we successfully identified the hemodynamic status in patients with TIA using combined resting-state BOLD-fMRI and ASL data. Twenty-four patients with normal arrival time and CBF were in Stage 0; fourteen patients who showed delay arrival time and normal CBF which indicated elevated CBV were in Stage I ; and the other thirteen patients who had both delayed arrival time and decreased CBF were in Stage II. The number of patients who suffered ischemic stroke or TIA symptoms in 1 year after MRI scan: four patients in Stage 0 (17.4%); three patients in Stage I (23.1%); five patients in Stage II (45.5%). As we expected, the patients in Stage II was at highest risk of subsequent ischemic attack when compared to other two stages.

In our study, we employed TSA approach with time shift range from −3TR to +3TR (±6.0 s) and whole brain global mean as reference time course (whole-brain reference, time shift range 3, WB3) which in accordance with previous studies [25–27]. Khalil and colleagues found the highest median correlation between MTT from DSC-PWI and TSA delay results using WB3. The authors also showed BOLD delay with WB3 had high sensitivity and specificity for predicting severe hypoperfusion [25]. These findings suggested that the time shift range and the reference time course which we employed for TSA approach in this study was reasonable.

In our study, all of ten patients with severe intracranial large-vessel stenosis/occlusion confirmed by MRA or carotid artery stenosis/occlusion identified by carotid duplex ultrasound examination showed considerable time delay areas. Recent study has found that TSA method could detect perfusion deficits comparable to that of DSC-PWI in subacute stage of ischemic stroke patients, especially in patients with large-vessel occlusion or stenosis [27]. This result was consistent with previous study which also indicated that PWI/DWI mismatch was always associated with a major vessel occlusion in acute phase of stroke [35]. Our results confirmed that TSA approach was sensitive to detect hypoperfusion due to severe major vessel stenosis/occlusion.

Patients in this study have a wide range of ages (30–79). Recent studies have indicated that approximately 10–14% of ischemic strokes occur in adults ages 18–45 years [36]. Nearly 18% of adults over 45 years experience at least one symptom of a TIA [22]. Only one patients was 30 years old who had transient neurologic symptoms due to a possible vascular etiology evaluated by experienced clinical neurologists. The other 50 patients were over 41 years, most of them (46) were over 45 years. We compared the age difference among patients in three different hemodynamic stages and found there were no significant difference in age (one-way ANOVA, $F=0.816$, $p=0.4488$).

Our study had several limitations. First, the telephone follow-up was not enough to monitor how the cerebral perfusion changes in patients with TIA. To be clinically helpful, the brain imaging should be acquired in the follow-up procedure to fully understand the hemodynamic status and predict the risk of subsequent events. Second, the results that patients who showed delay arrival time and normal CBF were in Stage I which characterizes elevated CBV need to be testified with actual CBV measured in the future. Another limiting factor in this study was head motion during resting-state BOLD-fMRI acquisition. Both the large head movements and large oscillation can affect the TSA results. Thus, to be clinically viable, effective ways to manage head motion, such as reducing scanning time or applying multi-band sequence during data acquisition, would be able to further improve the precision of hypoperfusion assessment.

Conclusions

This study demonstrated that resting-state BOLD-fMRI TSA method could detect perfusion deficits in patients with TIA. The combination of resting-state BOLD-fMRI and ASL hold the potential to noninvasively identify the hemodynamic status in TIA patients and help predict the risk of subsequent events (ischemic attack and stroke). Thus, the combination of two fMRI techniques could help diagnose and guide therapeutic decisions for patients with TIA.

Acknowledgements We thank two professional radiologists (Ni Ling and Chen Qian) for helping delineate the data. We thank all the patients and volunteers for participating in this study. This work was supported by grants from National Key R&D Program of China (No. 2017YFC1310000), National Natural Science Foundation of China (No. 81771911, 81301210, 81271652, 81520108016, 31471084, 81661148045), Dr. Zang is partly supported by "Qian Jiang Distinguished Professor" program.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standards This study was approved by the Ethics Committee of the Center for Cognition and Brain Disorders, Hangzhou Normal University. Written informed consent was obtained from each participant.

References

1. Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, Hatsukami TS, Higashida RT, Johnston SC, Kidwell CS, Lutsep HL, Miller E, Sacco RL (2009) Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke 40:2276–2293. https://doi.org/10.1161/STROKEAHA.108.192218
2. Giles MF, Rothwell PM (2007) Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. Lancet Neurol 6(12):1063–1072. https://doi.org/10.1016/S1474-4422(07)70274-0
3. Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, Sidney S (2007) Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet 369:283–292. https://doi.org/10.1016/S0140-6736(07)60150-0
4. Ay H, Oliveira-Filho J, Buonanno FS, Schaefer PW, Furie KL, Chang YC, Rordorf G, Schwamm LH, Gonzalez RG, Koroshetz WJ (2002) 'Footprints' of transient ischemic attacks: a diffusion-weighted MRI study. Cerebrovasc Dis 14:177–186. https://doi.org/10.1159/000065682
5. Giles MF, Albers GW, Amarenco P, Arsava EM, Asimos AW, Ay H, Calvet D, Coutts SB, Cucchiara BL, Demchuk AM, Johnston SC, Kelly PJ, Kim AS, Labreuche J, Lavallee PC, Mas JL, Merwick A, Olivot JM, Purroy F, Rosamond WD, Sciolla R, Rothwell PM (2011) Early stroke risk and ABCD2 score performance in tissue- vs time-defined TIA: a multicenter study. Neurology 77:1222–1228. https://doi.org/10.1212/WNL.0b013e3182309f91
6. Ay H, Arsava EM, Johnston SC, Vangel M, Schwamm LH, Furie KL, Koroshetz WJ, Sorensen AG (2009) Clinical- and imaging-based prediction of stroke risk after transient ischemic attack: the CIP model. Stroke 40:181–186. https://doi.org/10.1161/STROKEAHA.108.521476
7. Calvet D, Touze E, Oppenheim C, Turc G, Meder JF, Mas JL (2009) DWI lesions and TIA etiology improve the prediction of stroke after TIA. Stroke 40:187–192. https://doi.org/10.1161/STROKEAHA.108.515817
8. Coutts SB, Eliasziw M, Hill MD, Scott JN, Subramaniam S, Buchan AM, Demchuk AM (2008) An improved scoring system for identifying patients at high early risk of stroke and functional impairment after an acute transient ischemic attack or minor stroke. Int J Stroke 3:3–10. https://doi.org/10.1111/j.1747-4949.2008.00182.x
9. Giles MF, Albers GW, Amarenco P, Arsava MM, Asimos A, Ay H, Calvet D, Coutts SB, Cucchiara BL, Demchuk AM, Johnston SC, Kelly PJ, Kim AS, Labreuche J, Lavallee PC, Mas JL, Merwick A, Olivot JM, Purroy F, Rosamond WD, Sciolla R, Rothwell PM (2010) Addition of brain infarction to the ABCD2 Score (ABCD2I): a collaborative analysis of unpublished data on 4574 patients. Stroke 41:1907–1913. https://doi.org/10.1161/STROKEAHA.110.578971
10. Krol AL, Coutts SB, Simon JE, Hill MD, Sohn CH, Demchuk AM, Group VS (2005) Perfusion MRI abnormalities in speech or motor transient ischemic attack patients. Stroke 36:2487–2489. https://doi.org/10.1161/01.STR.0000185936.05516.fc
11. Menon BK, Demchuk AM (2011) Computed Tomography angiography in the assessment of patients with stroke/TIA. Neurohospitalist 1:187–199. https://doi.org/10.1177/1941874411418523
12. Mlynash M, Olivot JM, Tong DC, Lansberg MG, Eyngorn I, Kemp S, Moseley ME, Albers GW (2009) Yield of combined perfusion and diffusion MR imaging in hemispheric TIA. Neurology 72:1127–1133. https://doi.org/10.1212/01.wnl.0000340983.00152.69
13. Petersen ET, Zimine I, Ho YC, Golay X (2006) Non-invasive measurement of perfusion: a critical review of arterial spin labelling techniques. Br J Radiol 79:688–701. https://doi.org/10.1259/bjr/67705974
14. Prabhakaran S, Patel SK, Samuels J, McClenathan B, Mohammad Y, Lee VH (2011) Perfusion computed tomography in transient ischemic attack. Arch Neurol 68:85–89. https://doi.org/10.1001/archneurol.2010.320
15. Restrepo L, Jacobs MA, Barker PB, Wityk RJ (2004) Assessment of transient ischemic attack with diffusion- and perfusion-weighted imaging. AJNR Am J Neuroradiol 25:1645–1652
16. Tong T, Yao Z, Feng X (2011) Combined diffusion- and perfusion-weighted imaging: a new way for the assessment of hemispheric transient ischemic attack patients. Int J Dev Neurosci 29:63–69. https://doi.org/10.1016/j.ijdevneu.2010.09.002
17. Grubb RL Jr, Derdeyn CP, Fritsch SM, Carpenter DA, Yundt KD, Videen TO, Spitznagel EL, Powers WJ (1998) Importance of hemodynamic factors in the prognosis of symptomatic carotid occlusion. JAMA 280:1055–1060
18. Alsop DC, Detre JA (1996) Reduced transit-time sensitivity in noninvasive magnetic resonance imaging of human cerebral blood flow. J Cereb Blood Flow Metab 16:1236–1249. https://doi.org/10.1097/00004647-199611000-00019
19. Kleinman JT, Zaharchuk G, Mlynash M, Ogdie AA, Straka M, Lansberg MG, Schwartz NE, Kemp S, Bammer R, Albers GW, Olivot JM (2012) Automated perfusion imaging for the evaluation of transient ischemic attack. Stroke 43:1556–1560. https://doi.org/10.1161/STROKEAHA.111.644971
20. MacIntosh BJ, Lindsay AC, Kylintireas I, Kuker W, Gunther M, Robson MD, Kennedy J, Choudhury RP, Jezzard P (2010) Multiple inflow pulsed arterial spin-labeling reveals delays in the arterial arrival time in minor stroke and transient ischemic attack. AJNR Am J Neuroradiol 31:1892–1894. https://doi.org/10.3174/ajnr.A2008
21. Qiao XJ, Salamon N, Wang DJ, He R, Linetsky M, Ellingson BM, Pope WB (2013) Perfusion deficits detected by arterial spin-labeling in patients with TIA with negative diffusion and vascular imaging. AJNR Am J Neuroradiol 34:2125–2130. https://doi.org/10.3174/ajnr.A3551

22. Zaharchuk G, Olivot JM, Fischbein NJ, Bammer R, Straka M, Kleinman JT, Albers GW (2012) Arterial spin labeling imaging findings in transient ischemic attack patients: comparison with diffusion- and bolus perfusion-weighted imaging. Cerebrovasc Dis 34:221–228. https://doi.org/10.1159/000339682
23. Derdeyn CP, Grubb RL, Powers WJ (1999) Cerebral hemodynamic impairment: methods of measurement and association with stroke risk. Neurology 53:251–259. https://doi.org/10.1212/WNL.53.2.251
24. Kroll H, Zaharchuk G, Christen T, Heit JJ, Iv M (2017) Resting-state BOLD MRI for perfusion and ischemia. Top Magn Reson Imaging 26:91–96. https://doi.org/10.1097/RMR.0000000000000119
25. Khalil AA, Ostwaldt AC, Nierhaus T, Ganeshan R, Audebert HJ, Villringer K, Villringer A, Fiebach JB (2017) Relationship between changes in the temporal dynamics of the blood-oxygen-level-dependent signal and hypoperfusion in acute ischemic stroke. Stroke 48:925–931. https://doi.org/10.1161/STROKEAHA.116.015566
26. Lv Y, Margulies DS, Cameron Craddock R, Long X, Winter B, Gierhake D, Endres M, Villringer K, Fiebach J, Villringer A (2013) Identifying the perfusion deficit in acute stroke with resting-state functional magnetic resonance imaging. Ann Neurol 73:136–140. https://doi.org/10.1002/ana.23763
27. Ni L, Li J, Li W, Zhou F, Wang F, Schwarz CG, Liu R, Zhao H, Wu W, Zhang X, Li M, Yu H, Zhu B, Villringer A, Zang Y, Zhang B, Lv Y, Xu Y (2017) The value of resting-state functional MRI in subacute ischemic stroke: comparison with dynamic susceptibility contrast-enhanced perfusion MRI. Sci Rep 7:41586. https://doi.org/10.1038/srep41586
28. Amemiya S, Kunimatsu A, Saito N, Ohtomo K (2014) Cerebral hemodynamic impairment: assessment with resting-state functional MR imaging. Radiology 270:548–555. https://doi.org/10.1148/radiol.13130982
29. Schultz-Larsen K, Lomholt RK, Kreiner S (2007) Mini-mental status examination: a short form of MMSE was as accurate as the original MMSE in predicting dementia. J Clin Epidemiol 60:260–267. https://doi.org/10.1016/j.jclinepi.2006.06.008
30. Biswal B, Hudetz AG, Yetkin FZ, Haughton VM, Hyde JS (1997) Hypercapnia reversibly suppresses low-frequency fluctuations in the human motor cortex during rest using echo-planar MRI. J Cereb Blood Flow Metab 17:301–308. https://doi.org/10.1097/00004647-199703000-00007
31. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001) A default mode of brain function. Proc Natl Acad Sci USA 98:676–682. https://doi.org/10.1073/pnas.98.2.676
32. Villringer A, Dirnagl U (1995) Coupling of brain activity and cerebral blood flow: basis of functional neuroimaging. Cerebrovasc Brain Metab Rev 7:240–276
33. Bonakdarpour B, Parrish TB, Thompson CK (2007) Hemodynamic response function in patients with stroke-induced aphasia: implications for fMRI data analysis. Neuroimage 36:322–331. https://doi.org/10.1016/j.neuroimage.2007.02.035
34. Rossini PM, Altamura C, Ferretti A, Vernieri F, Zappasodi F, Caulo M, Pizzella V, Del Gratta C, Romani GL, Tecchio F (2004) Does cerebrovascular disease affect the coupling between neuronal activity and local haemodynamics? Brain 127:99–110. https://doi.org/10.1093/brain/awh012
35. Jansen O, Schellinger P, Fiebach J, Hacke W, Sartor K (1999) Early recanalisation in acute ischaemic stroke saves tissue at risk defined by MRI. Lancet 353:2036–2037. https://doi.org/10.1016/S0140-6736(99)01146-0
36. Ji R, Schwamm LH, Pervez MA, Singhal AB (2013) Ischemic stroke and transient ischemic attack in young adults: risk factors, diagnostic yield, neuroimaging, and thrombolysis. JAMA Neurol 70:51–57. https://doi.org/10.1001/jamaneurol.2013.575